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TITLE: ANALYTICAL AND CHARACTERIZATION STUDIES OF ORGANIC CHEMICALS, DRUGS, AND DRUG FORMULATION

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14. ABSTRACT

During the peri od October 22, 2009 to Oc tober 21, 2010, the proj ect personnel conti nued to perform chemi cal/physical analyses on bul k pharmaceuti cal substances and formul ated dr ug products, and to manufacture dosage formul ations of interest to the USAMRMC Drug Devel opment Program for parasi tic and infectious diseases, chemical and biological defense, etc. Speci fic obj ectives were to desi gn, devel op, val idate, and appl y methods to deter mine chemi cal and physi cal characteristics of t he bulk drugs, drug products, to det ermine their stability under defined conditions, and to coordinate and work with subcontractors to produce an intravenous dosage form of artesunate.

15. SUBJECT TERMS
Anti-Parasitic D rugs, C hemical D efense Agents, C hemical Analyses, Stabilit y Studies, Form ulation D evelopment, and Manufacture of an IV Drug Product

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INTRODUCTION

This annual report for Contract W81XWH-09-C-0022 covers the period from October 22, 2009 — October 21, 2010. The report consists of an overview of the major activities, a listing of the specific tasks performed and reports submitted, and description of special projects performed. The report also includes a listing of personnel receiving pay from this effort and a bibliography of all publications and meeting abstracts that resulted from this contract during the report period.

This contract is concerned with analytical, characterization, and stability studies of chemicals, drugs, and drug formulations, and with development and manufacture of dosage formulations. The studies are monitored by Mr. William Y. Ellis, the Contracting Officer Representative (COR), Chief, Department of Chemical Information, Division of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR).

The overall objective of this project is the operation of an analytical laboratory to determine the identity, purity, strength, quality, physical and chemical properties, and stability of bulk pharmaceutical substances and formulated drug products, and to develop and manufacture, in limited quantities, dosage formulations of interest of the USAMRMC Drug Development Program for parasitic and infectious diseases, chemical and biological defense, anti-viral studies, etc. Specific objectives are to design, develop, validate, and execute methods to determine the following characteristics of candidate bulk pharmaceutical substances and formulated drugs, and to develop and manufacture, in limited quantities, dosage formulations.

- Identity, purity, and strength;
- Stability;
- Other physical and chemical characteristics, including weight variation, content uniformity, and other such compendial requirements;
- Qualitative and quantitative determination of impurities;
- Develop and manufacture, in limited quantities, dosage formulations; and
- Special projects not covered by the above headings.

ANNUAL REPORT (2009-2010)

OVERVIEW

During the contract period October 22, 2009 to October 21, 2010, the main emphasis of our project work continues to center on coordinating and working with the selected subcontractors to produce a second and larger batch of artesunic acid IV drug product. Coordination required not only scheduling between us and the subcontractors, but scientific inputs from us were indispensible. Much of the communication was conducted by conference phone calls. Additionally, several visits were made to the principal subcontractor, Dalton Pharma Services, to ensure scientific and regulatory compliances. The selected subcontractors are:

Steris Isomedix Services is to perform the ethylene oxide sterilization of the bulk active pharmaceutical ingredient. Although Steris provided the same service in 2004 for the first batch of artesunic acid IV drug product, several changes were made to improve the handling and sterilization of a larger amount of bulk artesunic acid (AS).

Dalton Pharma Services is to fill 9,000 vials of sterile AS under cGMP aseptic condition, test and release the drug product, and to conduct stability studies under cGMP shelf-life and accelerated conditions.

Afton Scientific Corporation is to produce, under cGMP conditions, 10,500 vials of sterile phosphate dissolution medium, which is the second component of the artesunic acid IV drug product. Afton also served in this capacity in 2004 for the first batch of artesunic acid IV drug product, SRI batch # 14462-16.

A second emphasis of our project work is to maintain the acceptability of the first batch of artesunic acid IV drug product by continuing stability studies at -20°C and +5°C. Drug product units stored at these temperatures for 51 months and 48 months respectively, after they had been stored at ~20 months at 18-20°C, continue to pass the chemical, and sterility/endotoxin requirements. We continue to improve our sample preparation of the crucial chemical test, <USP 788> particulate for injection. The improvement was centered on minimizing agitation of the AS/phosphate mixture and on lengthening the air bubble dissipation time, prior to counting the particulates in the constituted solution.

The third emphasis is our core effort, which is to perform identity and assay on bulk drugs and drug products of interest to the Army.

SPECIFIC TASKS PERFORMED AND REPORTS SUBMITTED

During the contract period October 22, 2009 to October 21, 2010 , the following tasks were performed and the reports submitted to the COR:

1. WR001544;AU29291, Lot N577DK, chloroquine phosphate, Report No. 1236.

2. WR002975;BJ08241, Lot AP-X-45, primaquine phosphate, Report No. 1250.

3. WR002977;BU29526, amodiaquine HCl in combination drug ARSUAMOON, Report No. 1242.

4. WR100517;BU29517, doxycycline hyclate tablets, Report No.1248; BU29508, doxycycline hyclate capsules, Report No. 1249.

5. WR142490;BU29482, mefloquine HCl, Reschke-0882, 250-mg tablets, Report No. 1246; BU29491, mefloquine HCl, Bloom 2430, 250-mg tablets, Report No.1247.

6. WR229870;BU28672, stibogluconate solution, Report No. 1240.

7. WR256283;BR294878, SRI Batch #14462-16, chemical stability of an artesunic acid clinical dosage form stored 36 months at +5°C, Report No. 1234. Chemical stability of the same material stored 40 months at +5°C, Report No. 1237. Chemical stability of the same material stored 44 months at +5°C, Report No. 1243.

8. WR256283;BJ92510, stability study on Guilin Lot ZA070802, Artesunate for Injection, Report No. 1244.

9. WR256283; BU29535, Guilin artesunate tablets in combination drug ARSUAMOON, Report No. 1245.

10. WR256283;BU24950, assay of artesunic acid in Adams Pharmaceuticals 50-mg tablets, Report No. 1238.

11. WR270295;BU22894, pamaquine HCl, Report No. 1227.

12. WR279396:BQ29268, paromomycin/gentamicin 15%/0.5% ointment, Report No. 1233; BU23757, TEVA lot 2314-180A; and BU23748, TEVA Lot 2314-180B, paromomycin/gentamicin 15%/0.5% ointment, Report No. 1239.

13. WR308275;BS87475, cis-mirincamycin, Report No. 1228.

14. WR308276;BS87484 and BU23042, trans-mirincamycin, also Report No. 1228.

15. WR308336;BS88570, TEVA Lot 2314-113, 15% paromomycin cream, Report No. 1231; BU24450, TEVA Lot 2314-113, 15% paromomycin cream, Report No. 1232; BU26258, TEVA Lot 2680-159A, paromomycin/gentamicin 15%/0.5% cream, Report No. 1241.

16. WR279396;BU24441, a TEVA paromomycin/gentamicin 15%/0.5% cream, TEVA Lot 2314-180B, Report No. 1229.

17. WR308336;BS88570, a TEVA 15% paromomycin cream, TEVA Lot 2314-113, Report No. 1231.

SPECIAL PROJECTS

Considerable time and effort were spent in assaying samples of decoquinate, WR299958. Of the several samples received and assayed, all were highly impure, each containing approximately 50% decoquinate. Attempts to purify these samples proved unsuccessful because the principal impurity is likely isomeric to decoquinate and shows very similar physical and chemical characteristics.

Additional time and effort were spent in trying to obtain a high purity sample of decoquinate. All suppliers of this chemical have addresses in China, as did two of the highly impure samples we analyzed. From the several suppliers I contacted, I requested a sample for analysis prior to purchase. After many weeks of email exchanges, only one supplier agreed to submit a sample. This sample proved to be of high quality, having a purity comparable to that of our USP decoquinate reference standard. When we decided to purchase a 5-kg quantity of the same batch as the sample we analyzed, the agent, who is a trader in business for himself, wants payment up front, leaving us with no safeguard. Moreover, this agent does not have a commercial bank source to which we can wire payment. Currently, we are trying to work with the company with whom the agent trades.

PUBLICATIONS AND PRESENTATION

No publications appeared during this report period.

AWARDS

No awards were received during the report period.

PERSONNEL

A listing of personnel who received major contract support during the report period is as follows:

Peter Lim, P.I.
Ronald Spanggord, Assistant P.I.
Patrick Macauley, Chemist
Jennifer Wang, Chemist
Katherine Irwin, Chemist

A listing of subcontractors who received major contract support during the report period is as follows:

Dalton Pharma Services
Afton Scientific Corporation
Steris Isomedix Services

SUMMARY/CONCLUSIONS

Subcontractor Steris Isomedix Services successfully sterilized the artesunic acid active pharmaceutical ingredient.

Subcontractor Dalton Pharma Services successfully completed its manufacture and release of 9,000 vials of artesunate IV dosage form in March 2010.

Afton Scientific Corporation successfully completed its manufacture and release of 10,500 vials of the phosphate dissolution medium in February 2010.

Stability studies on both components commenced at Dalton in March 2010.

Results from continuing stability studies on the first batch of artesunate IV dosage form, SRI batch# 14462-16, stored at 5°C have shown stability for at least 48 months and enabled its clinical use to continue. Analogously, its storage at -21°C has shown stability for 51 months, also enabling its clinical use to continue.

The project team continues to provide solutions to the Army's analytical chemical problems.